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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,536	01/29/2001	William H.R. Langridge	12273-3	9620

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EXAMINER	
HILL, MYRON G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,536	LANGRIDGE ET AL.	
	Examiner	Art Unit	
	Myron G. Hill	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50- 86* is/are pending in the application.

4a) Of the above claim(s) *65- 68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50- 64, and 69- 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 24 November 2003 has been entered.

Claims 50- 64, and 69- 86 are under consideration.

Drawings

The drawings (two figures) submitted 21 January 2003 are accepted by the Draftsman.

Rejections Withdrawn

Rejections Withdrawn - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 63 and 64 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims were amended to remove the phrase starting with "upon" and add "when expressed in a plant cell". The rejection is withdrawn.

Rejections Withdrawn - 35 USC § 102

Claims 50, 51, 58 and 63 were rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez *et al.*

Applicant has amended the claims to require a fusion protein with the fusion on the C terminus. Because this is a different structure than disclosed by Gonzalez et al., the rejection no longer applies and is withdrawn.

Claim 52 was rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez *et al.* and Manson *et al.*

Applicant argues that the rejection based on Gonzalez *et al.* no longer applies.

The rejection is withdrawn because of the amendment.

Claims 53- 57 and 59- 62 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez *et al.* and Hajishengallis *et al.*

Applicant argues that the rejection based on Gonzalez *et al.* no longer applies.

The rejection is withdrawn because of the amendment.

Claims 64, and 69- 86 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalez *et al.*, Manson *et al.*, and Hajishengallis *et al.*

Applicant argues that the rejection based on Gonzalez *et al.* no longer applies.

The rejection is withdrawn because of the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 50- 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear in claim 50 what "first" is used to refer to a immunogenic antigen because there is no "second" recited in the claim. Claim 54 does not further limit claim 53 because there are only 2 subunits to CT and it is not clear what else is meant.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50- 64 and 69- 86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain antigens including cholera, E.

coli, and rotavirus, does not reasonably provide enablement for immunogenic antigens of all mammalian diseases that elicits a protective immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re* Wands, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The claims are drawn to immunogenic antigens of mammalian diseases that elicit a protective immune response that are expressed as fusion proteins of cholera toxin subunits.

The mucosal adjuvant/carrier properties of cholera toxin are known in the art as well as it being an oral immunogenic agent. Bacterial toxins and viral antigens are known as immunogenic antigens that confer a protective immune response such as enterotoxic E. *coli* and hepatitis B virus, as discussed in Manson and Arntzen (cited in art rejections). There are many other mammalian diseases that do not have known immunogenic antigens that can elicit a protective immune response. For example, there are many forms of cancer and autoimmune diseases that do not have defined antigens that confer protective immunity.

The specification provides guidance on the use of fusion proteins comprising cholera toxin and rotavirus and/or E. *coli*. There is no guidance on the treatment of other diseases such as cancer.

Furthermore, there is no teaching that the CTB fusion complexes will work as anything other than a mucosal antigen for administration orally.

The claims are drawn to immunogenic antigens of all mammalian diseases that elicit a protective immune response.

Thus, it would take undue experimentation to make the cholera toxin fusion complexes that elicit a protective immune response from an immunogenic antigen of many mammalian diseases where there is no art recognized protective immunogenic antigen.

Claim Rejections - 35 USC § 102

Claims 50 and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Arakawa *et al.*

Arakawa *et al.* teach a protein complex comprising 5 monomers of a CTB fusion protein with the fusion at the 3' end of the CTB and the antigen fused is a causal factor of a mammalian disease (abstract and Figures 1 and 3).

Therefore, claims 50 and 63 are anticipated by Arakawa *et al.*

Claim Rejections - 35 USC § 103

Claims 50, 51, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arakawa *et al.* as applied to claim 50 above, in view of Gonzalez *et al.*

Arakawa *et al.* as discussed above teach a protein complex of CTB fusion proteins.

Arakawa *et al.* do not teach rotavirus antigen or infectious enteric disease.

Gonzalez *et al.* teach a rotavirus antigen (an infectious enteric disease) as a fusion at the 5' end of CTB (abstract).

One of ordinary skill in the art at the time of invention would have been motivated to make the fusion of Gonzalez *et al.*, which did not induce neutralizing antibodies, as a 3' fusion of Arakawa *et al.* because Arakawa *et al.* show the fusion to induce a protective response in mice when fed potatoes that express the protein complex. One of ordinary skill in the art at the time of invention would know that CTB is a strong mucosal antigen/adjuvant. In both Gonzalez *et al.* and Arakawa *et al.,* the CTB fusion protein forms a pentamer and binds to the CTB gut receptor. One would know that the CTB fusions on the 3' or 5' termini retain the desirable properties of the CTB portion. One would expect success in making the 3' fusion of an antigen of a mammalian disease as a CTB fusion protein that elicits a protective response because Arakawa *et al.* teaches their construct can induce a protective response.

Thus, it would have been *prima facie* obvious to make the CTB fusion of Gonzalez et al. as a 3' fusion protein as taught by Arakawa *et al.* with the expectation of

success. Therefore, the instant invention is obvious over Arakawa *et al.* in view of Gonzalez *et al.*

Claims 50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arakawa *et al.* as applied to claim 50 above, in view of Manson *et al.* (TIBTECH September 1995 vol. 13: 388- 392).

The claims are drawn to a cholera toxin fusion protein complex with a immunogenic antigen from an enterotoxigentic *E. coli.*

Arakawa *et al.* teach 3' fusion proteins of CTB as discussed above.

Arakawa *et al.* does not teach enterotoxic *E. coli.*

Manson teaches that cholera and enterotoxigentic *E. coli* are important causes of diarrhea and mortality in developing countries, that the enterotoxin from *E. coli* is similar to cholera toxin in many respects, that both are excellent oral adjuvants that stimulate response to co- fed antigens, both antigens are immunogenic against a mammalian disease, and that they have the adjuvant effect at doses lower than what causes disease (section "E" pages 389- 391).

It would have been obvious to one skilled in the art at the time of invention to express enterotoxic *E. coli* antigens in a fusion protein using the techniques of Arakawa *et al.* and the knowledge that the antigen was immunogenic against a mammalian disease. One of skill in the art would have known the advantages of expressing multiple antigens in one source for use as a vaccine as taught by Arakawa *et al.* and the multiple protective immunogenic antigens taught by Manson *et al.* which include cholera toxin.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to produce a cholera toxin fusion protein that contained an enterotoxigentic *E. coli* antigen with an expectation of success. Therefore, the instant invention is obvious over Arakawa *et al.* in view of Manson *et al.*

Claims 50, 51, 53- 57 and 58- 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arakawa *et al.* in view of Gonzalez *et al.* as applied to claims 50, 51 and 58 above, and further in view of Hajishengallis *et al.*

Arakawa *et al.* and Gonzalez *et al.* teach a CTB fusion protein complex as discussed above.

Arakawa *et al.* and Gonzalez *et al.* do not teach an additional cholera toxin (CT) subunit or additional antigens.

Hajishengallis *et al.* disclose a CT fusion protein comprising the A2 subunit and an immunogenic antigen for a causal factor of a mammalian disease and that the A2 fusion forms a complex with CTB subunit (Figure 1, and paragraph spanning pages 4330- 4331).

One of ordinary skill in the art at the time of the invention would have motivated to combine cholera toxin subunit fusion proteins because they are known to form complexes (5xB and 1xA) and that each subunit (A or B) can be constructed with a different immunogenic antigen as taught by Arakawa *et al.*, Gonzalez *et al.*, and Hajishengallis *et al.*

Thus it would have been *prima facie* obvious to combine subunit A of cholera toxin fusion protein of Hajishengallis *et al.* with the CTB fusions of Arakawa *et al.* and Gonzalez *et al.* with the expectation of success in making the claimed product. Therefore, the instant invention is obvious over Arakawa *et al.* in view of Manson *et al.* and further in view of Hajishengallis *et al.*

Claims 50, 52, 64, and 69- 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arakawa *et al.* in view of Manson *et al.* as applied to claims 50 and 52 above, and further in view of both Gonzalez *et al.* and Hajishengallis *et al.*

Arakawa *et al.* in view of Manson *et al.* disclose a protein complex as discussed above.

Gonzalez *et al.* does teach cholera toxin fusion proteins with a protective antigen from a mammalian disease (rotavirus).

Gonzalez *et al.* does not teach an additional cholera toxin (CT) subunit or additional antigens.

Manson teaches benefits of CT as an oral adjuvant and can be used to express heterologous antigens and also teaches that both subunits can be expressed in plants to gain the enhanced effect of the holotoxin (section starting page 389, penultimate paragraph).

Hajishengallis discloses a CT fusion protein comprising the A2 subunit and an immunogenic antigen for a causal factor of a mammalian disease and that the A2 fusion forms a complex with CT B subunit (Figure 1, and paragraph spanning 4330- 4331).

One of ordinary skill in the art at the time of the invention would have been motivated to combine cholera toxin subunit fusion proteins because they are known to form complexes and the that each subunit can be constructed with a different immunogenic antigen as taught by Gonzalez and Hajishengallis and express them in plants.

Thus it would have been *prima facie* obvious to combine the subunits of Gonzalez and Hajishengallis in plants as taught by Manson with the expectation of success of making the claimed product. Therefore, the instant invention is obvious over Arakawa *et al.* in view of Manson *et al.*, and further in view of both Gonzalez *et al.* and Hajishengallis *et al.*

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Myron G. Hill whose telephone number is 703-308-4521. The examiner can normally be reached on 9am-6pm Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Myron G. Hill
Patent Examiner
December 22, 2003

JEFFREY STUCKER
PRIMARY EXAMINER